Lineage-Specific Hematopoietic Growth Factors

TO THE EDITOR: Kaushansky (May 11 issue)[1] reports that "more recent studies indicate that patients treated for breast cancer with cyclophosphamide and doxorubicin may have an increased risk of myelodysplasia or acute myelogenous leukemia if they have also received G-CSF [granulocyte colony-stimulating factor]." Among the studies cited, Smith et al.[2] found a positive association between the use and dose of G-CSF and the risk of secondary acute leukemia in patients receiving standard doses of anthracycline and dose-intensified cyclophosphamide (cumulative incidence of myelodysplasia or acute myelogenous leukemia at five years, 1.01 percent), but distinguishing the contribution of intensified therapy from that of therapy with G-CSF is often difficult. Conversely, Crump et al.[3] found no cases of secondary acute leukemia among patients given epirubicin-based adjuvant chemotherapy plus G-CSF, and Citron et al.[4] reported no correlation between the use of G-CSF and the incidence of secondary acute leukemia in 2005 patients randomly assigned to standard or dose-dense chemotherapy. In our experience,[5] the crude incidence of secondary acute leukemia after adjuvant high-dose epirubicin plus cyclophosphamide with G-CSF support was 0.41 percent. Above all, the leukemogenic hazards of G-CSF should always be weighed against its therapeutic benefits.

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TO THE EDITOR: Kaushansky states that "G-CSF has been found to increase the risk of acute myelogenous leukemia in patients with congenital neutropenia. . . . Since the introduction of G-CSF, patients with congenital neutropenia live longer, but a malignant myeloid disorder develops in approximately 10 percent. . . . [I]t is likely that the administration of G-CSF to patients with congenital neutropenia selects for cells with a mutation in the G-CSF receptor that enhances the proliferation of myeloid cells."

We have recently analyzed and reported on the risk of leukemia in patients with congenital neutropenia on the basis of the long-term follow-up of 374 patients, most of whom were treated with G-CSF for many years.[1] The cumulative incidence of myelodysplasia or acute myeloid leukemia in these patients was 21 percent after 10 years. The development of leukemia was associated with a poor response to G-CSF — that is, more than the median dose of 8 μg of G-CSF per day was required to achieve a less-than-median neutrophil response. We suggest that patients who are more severely affected, as reflected in a lesser response to G-CSF, have an intrinsic, rather than acquired, predisposition to the development of myelodysplasia or acute myelogenous leukemia. Furthermore, mutations of the G-CSF receptor occur only in some cases evolving into myelodysplasia or acute myelogenous leukemia, and long-term treatment with G-CSF is not associated with a risk of myelodysplasia or acute myelogenous leukemia in patients with other forms of severe chronic neutropenia treated with this cytokine. Although Kaushansky's hypothesis is intriguing, the clinical data suggest that the risk of leukemia is more complex than he suggests.

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genital neutropenia receiving long-term G-CSF therapy. Blood 2006;107:4628-35.

THE AUTHOR REPLIES: I appreciate the interest in my recent review by two groups who study the leukemogenic potential of G-CSF. Ferretti and colleagues point to the statement that patients treated for breast cancer with cyclophosphamide and doxorubicin may have an increased risk of myelodysplasia or acute myelogenous leukemia if they also receive G-CSF. They suggest that this increased risk might be due to the increased dose intensity of the chemotherapy used in the patients described by Smith et al.[1] Nevertheless, the observation that the relative risk of myelodysplasia or acute myelogenous leukemia was six times the expected rate if G-CSF was administered, coupled with similar reports, is, in my view, sufficient to indicate the need for diligent surveillance when G-CSF therapy is used in patients at risk for treatment-related myelodysplasia or acute myelogenous leukemia.

The incidence of myelodysplasia or acute myelogenous leukemia in children with congenital neutropenia treated with G-CSF is reported to be between 10 and 20 percent. This range includes the observations by Rosenberg et al.,[2] which appeared after the publication of my review. Dale and colleagues take issue with the statement that "G-CSF has been found to increase the risk of acute myelogenous leukemia in patients with congenital neutropenia." This statement may be too dogmatic, but I believe that a role for the cytokine in the pathogenesis of myelodysplasia or acute myelogenous leukemia is probable. It seems premature to rule out any role for the cytokine. For example, Donadieu et al.[3] found that the dose intensity of G-CSF is an important contributor to the risk of myelodysplasia or acute myelogenous leukemia among patients with congenital neutropenia.

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Budd–Chiari Syndrome and Factor V Leiden in a Neonate

TO THE EDITOR: A 2700-g male infant, born at 35 weeks of gestation by cesarean section, was found to have fetal ascites without apparent cause at 33 weeks of gestation. The mother had IgG antibodies but not IgM antibodies against cytomegalovirus (CMV). At birth, the baby had moderate hepatomegaly and mild ascites; the results of liver-function tests were normal, and serologic analysis for hepatitis was negative.

At 29 days after birth, the baby underwent surgery for an inguinal hernia. The postoperative course was complicated by increasing hepatomegaly and generalized edema. The baby was transferred to our hospital; CMV infection was ruled out by polymerase-chain-reaction analysis of urine, saliva, and blood, as were Niemann–Pick disease, other metabolic diseases, and lysosomal storage diseases. The degree of hepatosplenomegaly increased, and the Budd–Chiari syndrome was diagnosed by abdominal computed tomography performed 48 days after birth

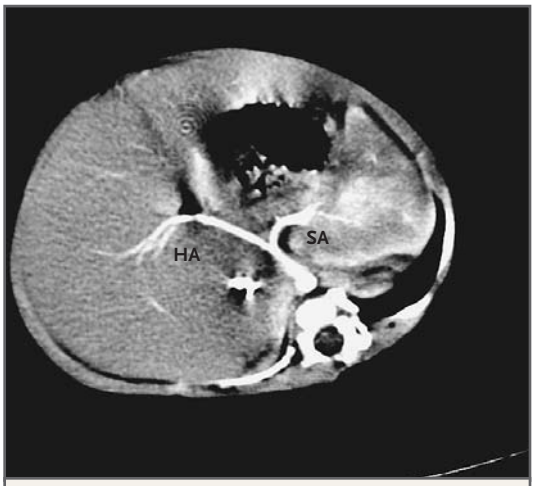

Figure 1. Abdominal CT Scan Showing Enlargement of the Liver and the Spleen in a 48-Day-Old Infant.
The celiac trunk, hepatic artery (HA), and splenic artery (SA) are filled with contrast medium, but the portal vein is not completely visualized.